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EXAMINER	
SIEW, JEFFREY	
ART UNIT	**PAPER NUMBER**
1637	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/634,352	CAO ET AL.	
	Examiner	Art Unit	
	Jeffrey Siew	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7,11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Request for Continued Examination

1. The request filed on 10/8/02 for a Request for Continued Examination (RCE) under 37 CFR 114 is acceptable. An action on the RCE follows.

The amendment filed 10/8/02 has been entered. Pending claims are 1-46.

2. The response filed 10/8/02 has been fully considered. The response has rebutted all the 102 and 103 rejections on the contention that the primary art reference of Freund is not enabling to derive nucleic acids from fewer than 1000 cells. As cited previously, Freund does state deriving nucleic acid and cDNA from a single cell col. 23 line 29. The response argues that the reference does not supply any technical disclosure as to the process of such derivation. Applicant is reminded that the claims do not recite any such specific type of process. The response further cites Genetech v. Novo Nordisk A/s 108 F.3d 1361, 42 USPQ2d 1001 (Fed Cir. 1997). There the court determined that omission of minor details does not cause specification to meet enablement. Moreover they noted that fact that no one had been able to produce any human protein via cleavable fusion expression as of application date of patent in suit undermines the patentee's contention that specification's disclosure of DNA sequence encoding human growth hormone and single example enzyme and its cleavage site, without more was enabling. In the instant case, a review of the prior art at the time of the invention was made **clearly shows a large number of references** detailing the state of art in deriving nucleic acids from single cells

e.g. Serafini et al 6,110,711Eberwine US5,514,545. Such evidence strongly suggests the **commonly practiced and well known knowledge** that the Genetech court referred to as minor details. However, as Freund et al statement that "it may be possible" in col. 23 line 29 may be argued to connote not an explicit teaching but rather strong motivation. New rejections with Eberwine prior art which is clearly enabling disclosure on deriving nucleic acids from single cells, are provided below.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3,5,9,14,18, 29-33,35-37,39 & 43 are rejected under under 35 U.S.C. 103(a) as being unpatentable over Friend et al (US6,203,987 March 20, 2001) in view of Eberwine (US5,514,545 May 7, 1996).

Friend et al teach gene expression monitoring using an array and classification (see whole doc. esp. abstract). They teach the basic principles of gene expression monitoring using the hybridization patterns on a microarray (see col. 1 line 16-50). They examine the cellular state of a plurality of cells or a single cell (see col. 1 line 64 and col. 23 line 29). The sample may be a cell, tissue, organ or multicellular organism (see col. 5 line 34). The mRNA transcripts of cell are examined by reverse transcription to DNA and bound to probes on a microarray (see col. 22 line 16-25). The probes may be between 50bp -2000bp. (see col. 24 line 35). They bind them to solid support such as glass, plastic (see col. 25 line4). The cDNA may labeled many of the well known and commonly practiced methods e.g. incorporations of fluorescently labeled dNTP or after synthesis they be labeled subsequently. A two color fluorescence labeling may be used to define alterations in the gene expression which allows the direct and internally controlled comparison of the mRNA levels corresponding to each arrayed gene in two cell states or to variations due to minor differences in experimental conditions (see col. 23 line17-32). They examine over 1000 genes (see col. 3 line 59). The hybridization the polynucleotides are perfectly matched (see col. 27 line 2). The method also has diagnostic purposes in examining tumors (see col. 18 line 64). They use a computer and software with a geneset database to classify the expression profile(see col. 20 line 20).

Freund et al does not explicitly teach the process of deriving from less than 1000 cells.

Eberwine et al explicitly teach deriving nucleic acids from a single cell to characterize cell identity or physiological state (see entire doc. esp. abstract). They teach the detailed process of deriving single cells through pipetting. (see example 1).

One of ordinary skill in the art would have been motivated to combine Eberwine et al's teaching of derivation of nucleic acids from single cells with Freund et al's method of analysis in order to compare drug treatment effect on cells. Freund et al explicitly states that using cDNA from single cells allows study of different effects of drugs or pathway perturbed cells and nontreated cells (see col.2 3 line 30-32). Moreover, Eberwine et al's states that their process allows the study of expression profiles with great specificity and sensitivity particularly neurons (see col.3 lines 64-65 & col. 1 lines 25-30). It would have been prima facie obvious to apply Eberwine et al's technique to Freund et al's expression array in order to successfully derive nucleic acids from single cells and examine the expression profile of single cells interactions.

4. Claims 12,15-17,19-22,24,27,28,34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friend et al (US6,203,987 March 20, 2001) in view of Eberwine (US5,514,545 May 7, 1996) in further view of Lockhart et al (Nature Biotechnology Vol. 14 pp. 1675-1660 Dec. 1996).

The teachings of Friend et al are described previously.

Friend et al do not mismatch probes, 10,000 genes and array density.

Lockhart et al teach expression monitoring by hybridization to high density oligonucleotide arrays (see whole doc. esp. abstract). They teach that high density containing 400,000 probes per area of 1.6cm^2. They teach 25mer probes. The array may cover 40,000 human genes (see page 1679). They teach signal intensity is linearly related to target concentration between 1:300,000 and 1:3000 (see Figure 3). They teach the use of ESTs on the probes.

One of ordinary skill in the art would have been motivated to apply Lockhart et al's method of expression monitoring to Friend et al in order to quantitatively and simultaneous monitor the genes in the human body. Lockhart et al's high density arrays would allow direct monitoring of large numbers of mRNAs in parallel (see abstract). It would have been prima facie obvious to apply Lockhart et al's array to Friend et al's method of expression monitoring and classification in order to classify the many different genes in the human body simultaneously.

5. Claims 4,7,8,10,11,13 & 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friend et al (US6,203,987 March 20, 2001) in view of Eberwine (US5,514,545 May 7, 1996) in further view of Hampson et al (US6,066,457 May 23, 2000).

The teachings and suggestions of Friend et al and Eberwine et al are described previously.

Friend et al do not teach transcripts of 500 base pair length.

Hampson et al teach creating cDNA of majority length of 100-500 base pairs (see whole doc. esp. col. 2 line 63).

One of ordinary skill in the art would have been motivated to apply Hampson et al's short transcripts to Friend et al's method of expression monitoring in order study differential gene expression. Hampson et al states that the short transcripts suitable for achieving uniform global PCR amplification representative of the original single stranded nucleic acid while maintaining correct strand sense. It would have been prima facie obvious to apply Hampson et al's method of producing short cDNA molecules to Friend et al's differential expression in order to obtain a representative sample of original mRNAs for accurate gene expression.

6. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Friend et al (US6,203,987 March 20, 2001) in view of Eberwine (US5,514,545 May 7, 1996) in further view of Van Ness et al (6,248,521 June 19, 2001).

The teachings and suggestions of Friend et al and Eberwine et al are described previously.

Friend et al do not teach incomplete extension by incorporation of ddNTP.

Van Ness et al teach that Tag based differential display allows amplification of partial cDNA sequences form subsets of mRNA from RT and PCR. This method allows direct comparison of two different cell types of samples (see whole doc. esp. col. 166 lines 18-33). They also teach ddNTP in primer extension reactions (see col. 17 line 1).

One of ordinary skill would have been motivated to employ ddNTPs in Van Ness method of differential display to Friend et al's array in order to compare different cell states. As ddNTP were well known chain terminators and would be expected to terminate the extension

products with an expected high degree of success, it would have been prima facie obvious to apply Van Ness et al's partial cDNA sequences to Friend et al's array in order to directly compare the expression of different cell types.

7. Claims 23,45 & 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friend et al (US6,203,987 March 20, 2001) in view of Eberwine (US5,514,545 May 7, 1996) in further view of Hampson et al (US6,066,457 May 23, 2000) and of North et al (6,114,502 Sept. 5, 2000).

The teachings and suggestions of Friend et al,Eberwine et al and Hampson et al are described previously.

Friend et al do not teach studying nueron type cells nor complete array.

North et al teach the study of genes that express proteins in the retinal and brain that are associated with neurosensory defect (see whole doc. esp. abstract). They also teach complete array to study the hybridization.(see col. 12 line 34-53).

One of ordinary skill in the art would have been motivated to apply North et al nucleic acid compositions to Friend et al's gene expression monitoring in order to examine the TULP expression in relationship to retinal dystrophies. As the expression was correlated with neurosensory defect, it would have been prima facie obvious to study the expression of North et al's TULP sequences in the Friend et al's array in order to identify the cells that express the sequences for diagnostic and therapeutic purposes.

8. Claims 38,40 & 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friend et al (US6,203,987 March 20, 2001) in view of Eberwine (US5,514,545 May 7, 1996) in further view of Dale (US6,087,112 July 12 ,2000).

The teachings and suggestions of Friend et al and Eberwine et al are described previously.

Friend et al do not teach cell differentiation.

Dale et al teach array hybridization differentiation (see col. 6 line 37).

One of ordinary skill in the art would have been motivated to apply Dale et al's teaching of cell differentiation to Friend et al's method of gene expression monitoring in order to identify the gene expression and gene to gene relationship during the biological process. It would have been prima facie obvious to study cell differentiation as taught by Dale to Friend et al's arrays in order to identify the expressed genes during differentiation or apoptosis.

9. Claim 44 is rejected under 35 U.S.C. 103(a) as being unpatentable over Friend et al (US6,203,987 March 20, 2001) in view of in view of Eberwine (US5,514,545 May 7, 1996) in further view of Hampson et al (US6,066,457 May 23, 2000) and North et al (6,114,502 Sept. 5, 2000) and Dale (US6,087,112 July 12 ,2000).

The teachings and suggestions of Friend et al,Eberwine et al and Hampson et al and North are described previously.

Friend et al do not teach studying nueron type of adult brain and differentiation.

Dale et al teach array hybridization differentiation (see col. 6 line 37).

One of ordinary skill in the art would have been motivated to apply Dale et al's teaching of cell differentiation to Friend et al's method of gene expression monitoring in order to identify the gene expression and gene to gene relationship during the biological process. It would have been prima facie obvious to study cell differentiation as taught by Dale to Friend et al's arrays in order to identify the expressed genes during differentiation as related to neuronal expression of TULP proteins as they were involved in many defects as taught by North et al..

10. Claims 25 & 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friend et al (US6,203,987 March 20, 2001) in view of Eberwine (US5,514,545 May 7, 1996) in further view of Scanlon (US5,814,489 Sept. 29, 1998).

The teachings and suggestions of Friend et al and Eberwine et al are described previously.

Friend et al do not teach incomplete extension by cleavage and end labeling.

Scanlon et al teach cleavage of amplification of mRNA and end labeling(see whole doc. esp. col. 4 lines 29-46)

One of ordinary skill in the art would have been motivated to cleave the amplification products of Friend et al and end label in order to detect changes in gene expression at the messenger level. As it was well known and commonly practiced in the art to end label fragment for detection it would have been prima facie obvious to amplify, cleave and end label fragments in Friend et al's assay in order to detect and identify specific mRNAs for gene expression monitoring.

SUMMARY

11. No claims allowed.

CONCLUSION

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Siew whose telephone number is (703) 305-3886 and whose e-mail address is Jeffrey.Siew@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner is on flex-time schedule and can best be reached on weekdays from 6:30 a.m. to 3 p.m. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119.

Any inquiry of a general nature, matching or filed papers or relating to the status of this application or proceeding should be directed to the Tracey Johnson for Art Unit 1637 whose telephone number is (703)-305-2982.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Center numbers for Group 1600 are Voice (703) 308-3290 and Before Final FAX (703) 872-9306 or After Final FAX (703) 30872-9307.

JEFFREY SIEW
PRIMARY EXAMINER

January 12, 2003